Clinical trial results:
ACE inhibition in Fontan patients: its effect on body fluid regulation.

Summary

EudraCT number	2016-004433-24
Trial protocol	NL
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	59498

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Trial Register: NL6415

Notes:

Sponsors

Sponsor organisation name	Leiden Universitair Medisch Centrum
Sponsor organisation address	Albinusdreef 2, Leiden, Netherlands,
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2019
Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To treat Fontan patients for 3 months with the ACE inhibitor enalapril and compare a set of cardiovascular measurements before and after treatment in order to study its effect on the cardiovascular system in Fontan patients.

Protection of trial subjects:

The examinations included in this study are low-impact and are not harmful to health. Most of the examinations are also well known by the patients as they are part of the regular checks. During the study, pain and distress were tried to be minimized, trial subjects could watch videos of their choice during the tilt table test, and a crème could be used to relieve the pain of blood sampling. There is a risk of falling of the tilting table, but this risk is minimized by properly securing the trial subjects to the table and always having a second person present during the tests. Furthermore, there is a risk of side effect from enalapril. During the entire study, trial subjects could easily contact the researchers, if side effects occurred, the dosage could easily be reduced or discontinued. Finally, trial subjects could leave the study at any time.

Background therapy:

Although survival of Fontan patients has improved, life expectancy is still less than normal, and many patients suffer from morbidities. Exercise performance, diastolic and systolic ventricular function are already reduced at a young age. Because severe diastolic and systolic dysfunction may not be present yet, both functions deteriorate over time in these patients, which may eventually result in heart failure. Enalapril, an angiotensin converting enzyme (ACE) inhibitor, has shown to be effective in reducing mortality in patients with a biventricular heart and mild to severe symptomatic heart failure. Therefore, ACE inhibition became the cornerstone of therapeutic interventions in patients with systolic heart failure. The effectiveness of ACE inhibition has been ascribed to its effect on various cardiovascular and pulmonary parameters, including systemic vascular resistance, cardiac autonomic tone, aortic pulse wave velocity (a surrogate of aortic stiffness) and lung function. However, the role of afterload reduction in Fontan patients for heart failure therapy is controversial. Many centers prescribe enalapril on a routine base for patients with a Fontan circulation and preserved ventricular function, while other centers have considerable doubt about its effectiveness as the systemic circulation in Fontan patients is highly preload dependent. In a small study no effect of enalapril on exercise capacity in Fontan patients has been found. There are yet no studies available that investigate the effect of ACE inhibition on various cardiovascular parameters in patients with a Fontan circulation. Studying the effects of short-term ACE-inhibition on several cardiovascular parameters will provide new insights on the effects of afterload reduction in Fontan patients.

Evidence for comparator:

We did not compare different therapies, we compared the parameters of patients before treatment at baseline with parameters after three months of enalapril treatment.

Actual start date of recruitment	10 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	20
Adolescents (12-17 years)	51
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients and healthy controls were recruited from July 2017 to October 2019. Fontan patients from 8 to 18 years old who were operated at the Leiden University Medical Center were recruited. Healthy controls with a similar age were recruited through advertising in local schools.

Pre-assignment

Screening details:

Patients with pre-existent ACE inhibitor use, systolic ventricular dysfunction and those unable to exercise were excluded. A total of 74 Fontan patients were eligible for inclusion of which 36 agreed to participate. 35 healthy controls were included.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Enalapril treatment baseline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Renitec:Enalapril
Investigational medicinal product code	CPMP/3175/03
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initial enalapril dosage was 5 mg/day and was titrated, as tolerated, to the target dose of 0.5 mg/kg/day or a maximum of 20 mg/day. Enalapril dosage was titrated by blood pressure measured weekly for at least 2 weeks after initiation of treatment.

Number of subjects in period 1[1]	Enalapril treatment baseline
Started	30
Completed	28
Not completed	2
Consent withdrawn by subject	1
Not completed because of non-compliance	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: It is correct that the numbers are not the same.
71 subjects were included, 36 Fontan patients and 35 controls. From the 36 Fontan patient 30 patients started with treatment.

Period 2	
Period 2 title	End of trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Enalapril treatment Follow-up
Arm description: Follow-up	
Arm type	Follow-up
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Enalapril treatment Follow-up
Started	28
Completed	28

Baseline characteristics

Reporting groups

Reporting group title	Enalapril treatment baseline

Reporting group description: -

Reporting group values	Enalapril treatment baseline	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	4	4	
Adolescents (12-17 years)	26	26	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	14.0		
inter-quartile range (Q1-Q3)	12.9 to 16.7	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	20	20	
Main ventricle Units: Subjects			
Left	15	15	
Right	12	12	
Undifferentiated	3	3	
Fenestration Units: Subjects			
Open at time of study	1	1	
Closed at time of study (naturally or by device)	27	27	
No fenestration	2	2	
Type Fontan tunnel Units: Subjects			
TCPC-EC	30	30	
TCPC-LT	0	0	
APC	0	0	
Age at Glenn operation Units: Years			
median	0.50		
inter-quartile range (Q1-Q3)	0.38 to 0.77	-	

Age at Fontan operation			
Units: Years			
arithmetic mean	3.11		
standard deviation	± 0.64	-	

Subject analysis sets

Subject analysis set title	All Fontan patients
Subject analysis set type	Full analysis
Subject analysis set description: Baseline	
Subject analysis set title	Healthy controls
Subject analysis set type	Full analysis
Subject analysis set description: Baseline	
Subject analysis set title	Fontan patient completed enalapril study baseline
Subject analysis set type	Per protocol

Subject analysis set description:

From the 36 patients, 6 patients only participated in the baseline measurements, therefore 30 patients were enrolled in the enalapril part of the study. During the study 1 patient withdrew at the request of parents and 1 patient was excluded for further analysis because of medication noncompliance.

Reporting group values	All Fontan patients	Healthy controls	Fontan patient completed enalapril study baseline
Number of subjects	36	35	28
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	6	14	3
Adolescents (12-17 years)	30	21	25
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	14.0	12.8	13.9
inter-quartile range (Q1-Q3)	12.7 to 16.6	11.1 to 15.5	13.0 to 16.7
Gender categorical Units: Subjects			
Female	13	17	10
Male	23	18	18
Main ventricle Units: Subjects			
Left	21	35	13
Right	12	0	12
Undifferentiated	3	0	3
Fenestration			

Units: Subjects			
Open at time of study	1	0	1
Closed at time of study (naturally or by device)	32	0	25
No fenestration	3	0	2
Type Fontan tunnel			
Units: Subjects			
TCPC-EC	36	0	28
TCPC-LT	0	0	0
APC	0	0	0
Age at Glenn operation			
Units: Years			
median	0.52	-	0.5
inter-quartile range (Q1-Q3)	0.38 to 0.79	- to -	0.37 to 0.75
Age at Fontan operation			
Units: Years			
arithmetic mean	3.19	-	3.10
standard deviation	± 0.65	±	± 0.60

End points

End points reporting groups

Reporting group title	Enalapril treatment baseline
Reporting group description: -	
Reporting group title	Enalapril treatment Follow-up
Reporting group description: Follow-up	
Subject analysis set title	All Fontan patients
Subject analysis set type	Full analysis
Subject analysis set description: Baseline	
Subject analysis set title	Healthy controls
Subject analysis set type	Full analysis
Subject analysis set description: Baseline	
Subject analysis set title	Fontan patient completed enalapril study baseline
Subject analysis set type	Per protocol
Subject analysis set description: From the 36 patients, 6 patients only participated in the baseline measurements, therefore 30 patients were enrolled in the enalapril part of the study. During the study 1 patient withdrew at the request of parents and 1 patient was excluded for further analysis because of medication noncompliance.	

Primary: Maximal oxygen consumption

End point title	Maximal oxygen consumption
End point description:	
End point type	Primary
End point timeframe: Measurements from baseline were compared with measurements acquired after a 3 month treatment period with enalapril.	

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: ml/kg/min				
arithmetic mean (standard deviation)	26.2 (± 4.7)	26.7 (± 6.5)		

Statistical analyses

Statistical analysis title	Maximal oxygen consumotion
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up

Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.691
Method	Paired-sample T-test

Primary: Heart rate variability RSA

End point title	Heart rate variability RSA

End point description:

End point type	Primary

End point timeframe:

Main analysis: Baseline vs 3 months of treatment
Sub-analysis: Baseline Fontan patients vs controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	21	28	34
Units: ms				
median (inter-quartile range (Q1-Q3))	81.5 (42.2 to 111.1)	66.7 (35.7 to 88.2)	68.7 (26.1 to 110.3)	84.5 (54.7 to 123.5)

Statistical analyses

Statistical analysis title	RSA treatment arm
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	equivalence[1]
P-value	= 0.476
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - 21 patients were compared in pairs

Statistical analysis title	RSA subanalysis

Statistical analysis description:

Sub analysis between Fontan patients and healthy controls

Comparison groups	All Fontan patients v Healthy controls

Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.104
Method	Wilcoxon (Mann-Whitney)

Primary: Pre-ejection period

End point title	Pre-ejection period

End point description:

End point type	Primary

End point timeframe:

Main analysis: Baseline vs 3 months of enalapril treatment
Sub analysis: Baseline measures Fontan patients vs healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	21	28	34
Units: ms				
arithmetic mean (standard deviation)	123.7 (± 17.8)	127.5 (± 3.9)	122.4 (± 17.6)	81.3 (± 15.9)

Statistical analyses

Statistical analysis title	PEP treatment arm
Comparison groups	Enalapril treatment Follow-up v Enalapril treatment baseline
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	equivalence[2]
P-value	= 0.141
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.88
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	2.45

Notes:

[2] - 21 patients before and after treatment were analyzes pair wise

Statistical analysis title	PEP subanalysis

Statistical analysis description:	
Comparing all Fontan patients with healthy controls	
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	41.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.5
upper limit	49.7
Variability estimate	Standard deviation
Dispersion value	4.29

Primary: Passive leg raising Cardiac index

End point title	Passive leg raising Cardiac index

End point description:

End point type	Primary

End point timeframe:

Main analysis: difference between cardiac index from baseline to passive leg compared between baseline and after 3 months of treatment
Subanalsysis: Difference in cardiac index change between all fontan patients and healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	16	16	21	34
Units: Percentage				
arithmetic mean (standard deviation)	0.62 (± 16.8)	-6.20 (± 8.4)	-1.17 (± 15.9)	-3.34 (± 16.6)

Statistical analyses

Statistical analysis title	Subanalysis

Statistical analysis description:

Comparison of change of cardiac index from baseline to passive leg raising between fontan patients and controls

Comparison groups	All Fontan patients v Healthy controls

Number of subjects included in analysis	55
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.52
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	10.55
Variability estimate	Standard error of the mean
Dispersion value	4.18

Statistical analysis title	PLR CI Enalapril anaysis

Statistical analysis description:

Comparing the difference in cardiac index form baseline lying to passive leg in patients before and after a three month enalapril treatment.

Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	32
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.06
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	14
Variability estimate	Standard deviation
Dispersion value	3.36

Primary: Passive leg raising cardiac autonomic tone RSA

End point title	Passive leg raising cardiac autonomic tone RSA

End point description:

End point type	Primary

End point timeframe:

Main comparison: Difference in RSA from baseline lying to passive leg raising in patient before and after three months of treatment with enalapril

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	21	28	34
Units: Percentage				
median (inter-quartile range (Q1-Q3))	0.59 (-10.3 to 22.9)	-4.59 (-17.9 to 11.7)	1.05 (-10.6 to 22.3)	1.64 (-15.0 to 14.9)

Statistical analyses

Statistical analysis title	Main comparison RSA enalapril treatment
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.149
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Subanalysis PLR RSA
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.777
Method	Wilcoxon (Mann-Whitney)

Primary: Head up tilt test cardiac index percentage change

End point title	Head up tilt test cardiac index percentage change

End point description:

End point type	Primary

End point timeframe:

Main comparison: Percentage difference from baseline lying to head up tilt testing in patients before and after three months of treatment
Sub analysis: the percentage difference in CI between Fontan patients at baseline and healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	20	32
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-6.69 (-18.2 to 2.43)	-20.51 (-27.6 to -6.8)	-9.69 (-18.3 to -4.6)	-17.95 (-24.6 to -3.1)

Statistical analyses

Statistical analysis title	HUT CI Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.027
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HUT CI subanalysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.221
Method	Wilcoxon (Mann-Whitney)

Primary: Head up tilt test Cardiac index absolute

End point title	Head up tilt test Cardiac index absolute

End point description:

End point type	Primary

End point timeframe:

Cardiac index at HUT before an after treatment with enalapril

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: L/min/m2				
arithmetic mean (standard deviation)	2.99 (± 0.49)	2.83 (± 0.69)		

Statistical analyses

Statistical analysis title	HUT CI enalapril absolute
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.153
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.39
Variability estimate	Standard error of the mean
Dispersion value	0.11

Primary: Head up tilt test cardiac autonomic tone RSA

End point title	Head up tilt test cardiac autonomic tone RSA

End point description:

End point type	Primary

End point timeframe:

Main parameter: Perc. difference of RSA from supine rest to head up tilt before and after three months of treatment
Sub analysis: Perc difference between fontan patients at baseline and healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	21	27	32
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-44.0 (-65.5 to -12.3)	-34.3 (-61.9 to -8.6)	-44.0 (-62.7 to -25.7)	-47.0 (-54.3 to -31.8)

Statistical analyses

Statistical analysis title	HUT RSA treatment
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.903
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	HUT RSA subanalysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	59
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.843
Method	Wilcoxon (Mann-Whitney)

Primary: Head up tilt test cardiac autonomic tone PEP

End point title	Head up tilt test cardiac autonomic tone PEP

End point description:

End point type	Primary

End point timeframe:

Main analysis: Perc. difference of PEP from supine rest to head up tilt test in patients before and after thee months of treatment
Sub analysis: Perc. difference between Fontan patients at baseline and healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	21	21	27	32
Units: Percentage				
median (inter-quartile range (Q1-Q3))	6.8 (-0.2 to 19.5)	5.6 (-1.3 to 20.0)	6.9 (0.3 to 16.9)	31.6 (16.0 to 61.1)

Statistical analyses

Statistical analysis title	HUT PEP enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up

Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.131
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Subanalysis HUT PEP
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	59
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Passive leg raising cardiac autonomic tone PEP

End point title	Passive leg raising cardiac autonomic tone PEP

End point description:

End point type	Primary

End point timeframe:

Main analysis: Perc. change in PEP from supine rest to PLR in patients before and after three months of treatment with enalapril

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	27	34
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-1.6 (-2.9 to 1.0)	-0.9 (-2.2 to 1.9)	-1.48 (-3.0 to 0.9)	-1.1 (-3.1 to 0.7)

Statistical analyses

Statistical analysis title	Sub analysis PLR PEP
Comparison groups	All Fontan patients v Healthy controls

Number of subjects included in analysis	61
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.717
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PLR PEP treatment
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.433
Method	Wilcoxon (Mann-Whitney)

Secondary: Systolic Global longitudinal strain

End point title	Systolic Global longitudinal strain

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline versus three moths of treatment with enalapril
Sub analysis: All Fontan patients vs healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	29	33
Units: Percentage				
arithmetic mean (standard deviation)	15.3 (± 3.5)	14.6 (± 3.1)	15.3 (± 3.2)	16.6 (± 2.4)

Statistical analyses

Statistical analysis title	Global longitudinal strain enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.139
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	1.71
Variability estimate	Standard error of the mean
Dispersion value	0.47

Statistical analysis title	Global longitnudinal strain sub analysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.062
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0.07
Variability estimate	Standard deviation
Dispersion value	0.71

Secondary: Systolic function TDI value free wall

End point title	Systolic function TDI value free wall

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril
Sub analysis: All Fontan patients vs health controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	27	27	36	33
Units: m/s				
arithmetic mean (standard deviation)	0.056 (± 0.01)	0.055 (± 0.01)	0.058 (± 0.02)	0.106 (± 0.03)

Statistical analyses

Statistical analysis title	TDI S free wall enalapril
Comparison groups	Enalapril treatment Follow-up v Enalapril treatment baseline
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.78
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.002

Statistical analysis title	TDI S free wall sub analysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	69
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	-0.038
Variability estimate	Standard deviation
Dispersion value	0.005

Secondary: Systolic function TDI IVS

End point title	Systolic function TDI IVS

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of enalapril treatment
Sub analysis: All Fontan patients vs healthy controls

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	32	34
Units: m/s				
median (inter-quartile range (Q1-Q3))	0.043 (0.03 to 0.05)	0.043 (0.04 to 0.05)	0.043 (0.03 to 0.05)	0.080 (0.07 to 0.08)

Statistical analyses

Statistical analysis title	TDi S IVS Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.875
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	TDI S IVS sub analsyis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Diastolic E/A

End point title	Diastolic E/A

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients
Sub analysis: Baseline all Fontan patients vs healthy controls.

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	24	36	35
Units: Not applicable				
median (inter-quartile range (Q1-Q3))	1.43 (1.1 to 1.9)	1.51 (1.2 to 1.9)	1.43 (1.1 to 2.1)	2.32 (2.0 to 2.7)

Statistical analyses

Statistical analysis title	Diastolic E/A Sub analysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	71
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diastolic E/A Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.361
Method	Wilcoxon (Mann-Whitney)

Secondary: Diastolic E/E'

End point title	Diastolic E/E'

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients
Sub analysis: Baseline all Fontan patients vs healthy controls.

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	24	36	34
Units: Not applicable				
median (inter-quartile range (Q1-Q3))	8.79 (6.7 to	7.70 (7.3 to	8.51 (6.49 to	5.71 (5.1 to

11.9)	11.7)	12.5)	7.1)

Statistical analyses

Statistical analysis title	Diastolic E/E Enalapril
Comparison groups	Enalapril treatment Follow-up v Enalapril treatment baseline
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.864
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Diastolic E/E subanalysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	70
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Submaximal exercise VE/VCO2

End point title	Submaximal exercise VE/VCO2

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Not applicable				
median (inter-quartile range (Q1-Q3))	36.1 (32.6 to 40.8)	38.1 (34.1 to 42.5)		

Statistical analyses

Statistical analysis title	Submaximal exercise VE/VCO2
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.133
Method	Wilcoxon (Mann-Whitney)

Secondary: Submaximal exercise OUES/kg

End point title	Submaximal exercise OUES/kg

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Not apllicable				
arithmetic mean (standard deviation)	27.2 (± 6.0)	26.9 (± 6.5)		

Statistical analyses

Statistical analysis title	Submaximal exercise OUES/kg
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.706
Method	t-test, 2-sided

Secondary: Blood NT-pro BNP

End point title	Blood NT-pro BNP

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: ng/L				
median (inter-quartile range (Q1-Q3))	80.2 (48.4 to 146.8)	71.5 (42.1 to 136.4)		

Statistical analyses

Statistical analysis title	Blood NT Pro BNP Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)

Secondary: Aortic stiffnes PWVao

End point title	Aortic stiffnes PWVao

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients
Sub analysis: Baseline all Fontan patients vs healthy controls.

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	31	34
Units: m/s				
arithmetic mean (standard deviation)	5.3 (± 0.9)	5.2 (± 1.2)	5.5 (± 1.1)	4.7 (± 0.6)

Statistical analyses

Statistical analysis title	Aortic stiffness PWVao Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.535
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Aortic stiffness PWVao Sub analysis
Comparison groups	Healthy controls v All Fontan patients
Number of subjects included in analysis	65
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.32
Variability estimate	Standard deviation
Dispersion value	0.22

Secondary: Aortic stiffness AIXao

End point title	Aortic stiffness AIXao

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients
Sub analysis: Baseline all Fontan patients vs healthy controls.

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	31	34
Units: Percentage				
arithmetic mean (standard deviation)	19.4 (± 9.7)	17.0 (± 9.8)	17.5 (± 9.9)	11.2 (± 7.8)

Statistical analyses

Statistical analysis title	Aortic stiffness AIXao Sub analysis
Comparison groups	All Fontan patients v Healthy controls
Number of subjects included in analysis	65
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.006
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.85
upper limit	10.7
Variability estimate	Standard deviation
Dispersion value	2.2

Statistical analysis title	Aortic stiffness AIXao Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.062
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	4.98
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Central systolic blood pressure

End point title	Central systolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

Main: Baseline vs three months of treatment with enalapril in Fontan patients
Sub analysis: Baseline all Fontan patients vs healthy controls.

End point values	Enalapril treatment baseline	Enalapril treatment Follow-up	All Fontan patients	Healthy controls
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	34	35
Units: mmHg				
arithmetic mean (standard deviation)	109.9 (± 9.6)	104.3 (± 9.2)	118.8 (± 9.1)	108.9 (± 8.6)

Statistical analyses

Statistical analysis title	Central systolic blood pressure Enalapril
Comparison groups	Enalapril treatment baseline v Enalapril treatment Follow-up
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.003
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	9.1
Variability estimate	Standard error of the mean
Dispersion value	1.67

Statistical analysis title	Central systolic blood pressure Sub analysis
Comparison groups	All Fontan patients v Healthy controls

Number of subjects included in analysis	69
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	14.1
Variability estimate	Standard deviation
Dispersion value	2.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First patient started with enalapril 19-09-2017 and last patient ended the study with enalapril on 21-10-2019

Adverse event reporting additional description:

Enalapril was titrated during the first weeks, if systolic blood pressure fell >20%, or if patients experienced side effects, dosage was lowered. Renal function was checked after 4-5 weeks. At baseline, during the titration period and at follow-up, patients were asked about side effects.

Assessment type	Systematic

Dictionary used

Dictionary name	METC / CCMO
Dictionary version	NA

Reporting groups

Reporting group title	Enalapril treatment

Reporting group description:

All Fontan patients who were treated with enalapril correctly. 30 patients were enrolled study and started with enalapril treatment. During the study 1 patient withdrew at the request of parents after a few weeks and 1 patient was excluded for further analysis because of medication noncompliance.

Serious adverse events	Enalapril treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Enalapril treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 30 (43.33%)		
Cardiac disorders			
Decrease >20% blood pressure	Additional description: Enalapril was titrated on blood pressure, when it fell >20% dosage was lowered, in all patients who experienced the blood pressure drop, blood pressure recovered with lowering the dosage and all patients completed the study with a lower dosage.		
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Syncope	Additional description: Two patients experienced syncope, after lowering the dosage it did not occurred again and both patients completed the study.		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Dizziness postural	Additional description: 3 patients experienced dizziness, in 2 patients it was related with enalapril and the dosage was lowered and it did not occur again. For he third patients it happened during a hot summer, after advise of extra fluid intake it did not happen again.		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Palpitations	Additional description: One patients, already known with palpitations before the study, experienced palpitations during the titration period, the dosage was not raised per protocol and the subject completed the study.		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Lower saturation, tired, cough	Additional description: 1 patient catched a cold cough during the study and due to the infection he was tired and had lower saturations, on parents request the patients stopped with the study.		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2019	An substantial amendment was done as: - We decided that healthy subjects did not had to do the exercise tests since sufficient reference values are already known in children to be able to compare the outcome values of the Fontan patients. - The diary used for the 24-hour VU-AMS measurement had not been submitted as a separated document at the firs submission. Therefore we added that at the amendment. - An example letter to the general practitioner about the participation of study patients was missing in the study file, we added that in the amendment. - In view of the changes of the privacy law in Europe, the trial subject information forms were adapted accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Small sample size despite many eligible patients. Nonetheless, this is the largest prospective study of enalapril in Fontan patients yet, and the power to conclude that enalapril has no beneficial effect was enhanced by lower-than-expected variance.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34375703